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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,414	SHARMA ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,5,9,10,16-19,23,28-30 and 32-35* is/are pending in the application.

4a) Of the above claim(s) *16-19,23,28-30 and 32-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/2/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed 10/3/2008.

The objection to the specification for having hyperlinks has been withdrawn.

The New Matter and Written Description rejections have been withdrawn upon further consideration.

The objection to the claims has been withdrawn in light of the amendment.

Claims 2, 4-5, 9, 13, 16-19, 23, 28-30, 32-35 are pending.

Claims 16-19, 23, 28-30, 32-35 have been withdrawn.

Claims 2, 4-5, 9, 13 are under examination.

Response to Amendment

1. The Declaration under 37 CFR 1.132 filed 10/3/2008 is insufficient to overcome the rejection of claims 2, 4-5, 9, 13 based upon the enablement rejection as set forth in the last Office action because: the declaration is of different scope than the claimed invention. This declaration is more fully addressed in the response to arguments of the enablement rejection.

Sequence compliance

2. The application fails to comply with CFR 1.821(c) and (d), which states:

> (c) Patent applications which contain disclosures of nucleotide and/or amino acid sequences must contain, as a separate part of the disclosure, a paper or compact disc copy (see § 1.52(e)) disclosing the nucleotide and/or amino acid sequences and associated information using the symbols and format in accordance with the requirements of §§ 1.822 and 1.823. This paper or compact disc copy is referred to elsewhere in this subpart as the "Sequence Listing." Each sequence disclosed must appear separately in the "Sequence Listing." Each sequence set forth in the "Sequence Listing" must be assigned a

separate sequence identifier. The sequence identifiers must begin with 1 and increase sequentially by integers. If no sequence is present for a sequence identifier, the code "000" must be used in place of the sequence. The response for the numeric identifier <160> must include the total number of SEQ ID NOs, whether followed by a sequence or by the code "000."

(d)Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

For example, page 89, the first line, refers to SEQ ID NO 1231, however the sequence listing only contains SEQ ID NO 1-501. It is noted that the tables contain numerous SEQ ID NO that correspond to nucleic acid sequence other than the 501 listed in the sequence listing.

It is further noted that the specification contains "Sequence ID 502" on page 166-SEQ ID NO 1495 on page 278 that do not appear to be present in the sequence listing.

It is further noted that the specification teaches SEQ ID NO G6 on page 278. G6 is an improper sequence identifier.

Applicant is required to check the rest of the disclosure for any other nucleic acid or protein sequences and list them in a sequence listing and identify them with a proper SEQ ID NO.

The specification and sequence listing must be amended to bring it into sequence compliance. **For any response to this office action to be fully compliant, the response has to bring the application in compliance with sequence rules.**

Response to Arguments

In view of the New Matter objection to the specification, the specification is viewed as not being sequence compliant.

Information Disclosure Statement

3. The information disclosure statement filed 10/2/2007 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Response to Arguments

Examiner has initialed the Liew, but has crossed out Fukioka, as no copy of Fukioka is of record.

Specification-New Grounds

4. The amendment filed 10/3/2008 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. MPEP 2163.07 II states: An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction. In re Odd, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971).

The added material which is not supported by the original disclosure is as follows:

The amended table 1a of 10/3/2008 lists clone ID I-24 as having 371 nucleotides and corresponding to SEQ ID NO11. The specification of 5/19/2005 lists in table 1a that I-24 is SEQ ID 308 and also has 373 nucleotides. SEQ ID NO 11 and SEQ ID NO 308 although having the same number of nucleotides have different sequences. Further the amendment of 10/3/2008 lists clone ID V-61 as SEQ ID NO 308 and the specification of 5/19/2005 lists V-61 as SEQ ID NO 721. Thus the amendment of 10/3/2008 has entered New Matter in the specification as the 10/3/2008 specification has changed numerous nucleotide sequence exemplified by I-24 and V-61, above and the artisan would not recognize the obvious error in the specification as the previous SEQ ID NO corresponded to sequences present in the CRF of the disclosure. Further there is nothing of record suggesting that switching the SEQ ID NO is an obvious correction.

Further instant table 1 a has deleted references to 156 clones including but not limited to ID I-01, I-02, I-13 are informative for disease diagnosis. This deletion appears to contradict the initial disclosure that these probes were informative, thus changing the scope of the disclosure.

Further Table 2 b has deleted references to clone 60 clone ID including I-52 are informative for diagnosis of breast cancer. This deletion appears to contradict the initial disclosure that these probes were informative, thus changing the scope of the disclosure. Additional as described for table 1 the clone ID of the instant amendment now correspond to different SEQ ID NO.

Further table 3 has deleted reference to reference 60 clone ID including all those listed for the 30% level in the specification of 5/19/2005. This deletion appears to

contradict the initial disclosure that these probes were informative, thus changing the scope of the disclosure. Additional as described for table 1 the clone ID of the instant amendment now correspond to different SEQ ID NO.

Further Table 4a has deleted references to clone 103 clone ID including I-01, I-02, I-03 are informative for diagnosis of Alzheimer's in the specification of 5/19/2005. This deletion appears to contradict the initial disclosure that these probes were informative, thus changing the scope of the disclosure. Additional as described for table 1 the clone ID of the instant amendment now correspond to different SEQ ID NO.

The instant amendment to table 4 b has changed the SEQ ID NO associated with each clone ID similar to as was done Table 1

The instant amendment to table 9 has changed the SEQ ID NO associated with each clone ID similar to as was done Table 1

Thus as all the deletions of clone ID NO and switching of SEQ ID NO was not an obvious error nor are the deletions or switching of SEQ ID NO obvious corrections, the amendments are new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2, 4-5, 9 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is drawn to the use of the claimed 351 oligonucleotide probes.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

Amended claim 2 is drawn to a set of oligonucleotide probes consisting of not more than 1000 oligonucleotides and said set comprising the 351 oligonucleotides having the sequences set forth in the recited SEQ ID NO, with the proviso that any of the said 351 oligonucleotides may be replaced with (i) an oligonucleotide fragment of

the respective oligonucleotide being replaced, which fragment is at least 15 nucleotides in length; (ii) an oligonucleotide having a sequence entirely complementary to the respective oligonucleotide being replaced, or to a fragment thereof which is at least 10 nucleotides in length or (iii) an oligonucleotide having at least 80% identity to the respective oligonucleotide being replaced or to a fragment thereof which is at least 10 nucleotides in length.

Thus (i) is drawn to replacing the oligonucleotide with "any" oligonucleotide fragment of respective oligonucleotide being replaced, which fragment is at least 15 nucleotides in length. Thus the claim broadly encompasses replacing "any" fragment of oligonucleotides claimed by SEQ ID NO with any fragment that is at least 15 nucleotides in length. This broadly encompass replacing any oligonucleotide with any other oligonucleotide.

Thus (ii) requires a sequence that is entirely complementary to the oligonucleotides claimed by SEQ ID NO or any fragment that is at least 10 nucleotides in length.

Thus (iii) requires an oligonucleotide having at least 80% identity to the respective nucleotide being replaced or a fragment thereof which is at least 10 nucleotides in length.

For the specification to be enabling for the set of oligonucleotide probes claimed, it must teach how to use the probe set for diagnosis of disease.

The amount of direction or guidance and the Presence and absence of working examples.

The specification, "different sets of probes may be used in techniques to prepare gene expression patterns and identify, diagnose or monitor different states, such as diseases, conditions or stages thereof" (see page 1, 1st paragraph).

The specification teaches, "we now describe probes and sets of probes derived from cells which are not disease cells and which have not contacted disease cells, which correspond to genes which exhibit altered expression in normal versus disease individuals, for use in methods of identifying, diagnosing or monitoring certain conditions, particularly diseases or stages thereof" (see last paragraph page 4 to top of page 5).

Example 1 of the specification teaches on page 64 that 497 genes were eliminated and 938 genes remained that were normalized to different external controls (page 65). The specification teaches that correct prediction was obtained in most breast cancer cell lines (page 65). The specification teaches on page 65 that this model correctly identified 41 of 46 non cancer samples (page 65). Thus example 1 of the instant specification suggests that 938 genes can be used to identify breast cancer. It is noted that the specification does not specifically recite with respect to example 1 which 938 probes were informative. Further is noted that Table 6 asserts that from 23 to 139 probes were used as diagnostic, but states an error rate of between 13 and 20%.

Example 2 of the specification teaches that an array of 758 cDNA clones were used instead of the 1435 probes in example 1 (page 67). The specification does not teach the number of the 758 cDNA clones required to be predictive, but notes in table 7

that none of the 14 subjects analyzed were predicted to have Alzheimer's by the method.

Example 3 of the specification a classification model that is generated by using 719 cDNA (page 71). The specification teaches that 111 of the 719 cDNA are described in Table 2 (page 71).

Example 3 of the specification teaches that 730 cDNA clones were picked and 520 probes were sequenced (page 73).

The specification does not provide examples of replacing any SEQ ID NO with fragments of cited SEQ ID NO or sequences that are 80% identical to the fragments.

The specification teaches that SEQ ID NO 268 is a 683 nucleotide sequence with numerous N (degenerate nucleotides) including a long stretch from position 506 to 514, 516 to 524, and 527 to 540.

The specification teaches that SEQ ID NO 389 a sequences of 601 nucleotids that has numerous N (degenerate nucleotides) including at positions 16-20, 87-89, 91-94, 120-122, 129-130, 228-229, 261-263, 267-268, 278-279.

The state of prior art and the predictability or unpredictability of the art:

The art of Cheung et al (Nature Genetics, 2003, volume 33, pages 422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of

17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3).

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of Pathology, 2001, volume 195, pages 53-65). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The prior art of Newton et al (Journal of Computational Biology, 2001, volume 8, pages 37-52) further teaches the difficulty in applying gene expression results. Newton et al teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph).

Draghici et al (Trends in Genetics (2006) volume 22, pages 101-109) that shortening probes from 30 nucleotides to 25 nucleotides reduces the sensitivity 10 fold (page 103, 1st column, 1st full paragraph). Draghici teaches that splice variant introduce variation in microarrays as short probes to not correctly identify the expression of all splice variants , while long probes will detect all variants (page 107, 2nd Column, 2nd

paragraph). Draghici teaches that a limited amount of complementarity can be sufficient to enable binding of two unrelated sequences (page 107, 2nd column, last paragraph).

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to determine if one of skill in the art could make and predictably use the invention as claimed. Thus the artisan would have to determine if the claimed collection of oligonucleotides would allow detection or diagnosis of breast cancer or Alzheimer's as asserted in the specification.

Embodiment (i) is drawn to replacing the oligonucleotide with "any" oligonucleotide fragment of respective oligonucleotide being replaced, which fragment is at least 15 nucleotides in length. Thus the claim broadly encompasses replacing "any" fragment of oligonucleotides claimed by SEQ ID NO with any fragment that is at least 15 nucleotides in length. Thus embodiment (i) of claim 1 broadly encompasses any nucleic acid, as it is replacing any fragment of SEQ ID NO with any oligonucleotide that is at least 15 nucleotides in length. This encompasses using any nucleic acid sequence. There is nothing of record in the specification or art suggesting a combination of any 351 oligonucleotide probes allows for diagnosis of any disease.

Embodiment (ii) is broadly drawn to replacing any oligonucleotide with an oligonucleotide that is completely complementary or a complementary fragment that is at least 10 nucleotides in length. It would be unpredictable to use a fragment of less

than complementary to the whole sequence as Draghici teaches that specificity decreases with length and that shorter probes do not hybridize all splice variants, thus probes of different lengths unpredictable as they would produce different results then the probes used because of splice variants and cross hybridization.

Embodiment (iii) of claim 2 is drawn to using a nucleic acid sequence that has 80% identity to the claimed sequences or fragments thereof which is at least 10 nucleotides in length. The specification teaches multiple sequences which contain degenerate nucleotides. The specification specifically teaches SEQ ID NO 268 which contains 35 nucleotides from position 506 to position 540, of which 3 were identified as being known. Thus any 10mer to 35mer could function as a probe for SEQ ID NO 268 for this region as claimed. There is no indication in the art or specification that a probe containing 10 to 35 nucleotides would allow predictable detection of "any" disease. Further SEQ ID NO 389 comprises at least 9 dinucleotide sequences that can be any bases (as represented by NN in the sequence listing), thus for a probe to be a fragment that is at least 10 bases and 80% identical to the sequence it would have to have 6 bases that are specific. It would be unpredictable for such short sequence as 6 base sequence occurs randomly in the genome an enormous number of times, further it would be unpredictable in view of the teachings of Draghici, that short probe will not detect splice variants that long probes detect.

Further it would be unpredictable in that the artisan would first have to determine which nucleic acids are informative in the instant method. This would be unpredictable in view of the New Matter rejection. The specification filed on 5/19/2005 suggested

informative probes identified by clone IDs and SEQ ID NO in the tables; the amendment of 10/3/2008 identifies clone ID No correspond to different SEQ ID NO. Further the amendment has deleted reference to over 100 clones, suggesting these clones are not informative, contrary to the initial filing. It would thus be unpredictable to use a collection of probes for detection or diagnosis of a disease without knowledge of which probes are truly informative.

This would be replete with unpredictable trial and error analysis because the specification does not how the expressed probe set is used to diagnose disease. Specifically the specification has in tables 1a, 1b, 2a, 2 b, 4 and 9 of the specification identify sequences that are informative of a disease state, breast cancer, Alzheimer's or Alzheimer's and breast cancer, however the specification does not teach how the combination of SEQ ID NO diagnose Alzheimer's or breast cancer. Thus the skilled artisan would have to determine if all the claimed capture probes or a specific subcombination of probes would have to demonstrate an increase or decrease expression to result in the diagnosis of any disease or Alzheimer's or breast cancer. This would be further unpredictable as the various tables do not recite that the claimed genes are informative.

Response to Arguments

The response traverse the enablement rejection by summarizing the previously presented rejection on pages 19-21 of response.

The response states:

Initially, Applicants note that "[d]etailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to

permit those skilled in the art to make and use the invention" (see M.P.E.P. §2164) "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim" (see M.P.E.P. §2164.01(b)).

The response continues citing the decision in Ex Parte Kubin that experimentation may be complex, but that does not necessarily make it undue and again quotes MPEP 2164.

The specification then asserts that large-scale gene expression analysis is known and routinely used in clinical biological arts for diagnosis of disease and cites the teachings of Orr. First it is noted that Orr is a review article and teaches that an array study identified possible differential regulation of genes in cell culture in response to a drug (page 475, 2nd column). This is thus of different scope than using a microarray to diagnose disease as it is perturbing a system and looking for a response, not examining subtle differences that occur over time, maybe even decades in Alzheimer's. Further on page 476 Orr teaches, "A variety of traditional techniques such as Q-RT-PCR and Northern analysis are used to confirm the gene expression modulations observed by microarray analysis. Furthermore, differential expression at the protein level for the gene of interest is required as well, as alterations in message levels do not always reflect a similar level of differential expression of the protein. A classical example for a lack of agreement between message and protein levels has been extensively documented for the p53 tumor suppressor protein that acquires post-translational modifications following cellular perturbations, such as DNA damage increasing protein levels without alterations in the expression levels of the message." Thus Orr does not

suggest it is predictable to use an array alone, but suggest data obtained from an array must be verified. Further the post filing art of Draghici teaches, "However, the multi-genic disease classifiers published so far do not seem to be consistent across studies used to predict the clinical outcome for the same type of cancer. For example, two groups attempted to develop a prognostic signature to predict survival in diffuse large B-cell lymphoma using different microarray platforms. The studies produced two completely different gene classifiers with 13 and 17 genes each, without a single overlapping gene between them . Similar inconsistencies were found in studies that aimed to develop gene-expression classifiers to predict the likelihood of distant metastasis in breast cancer"(box 2). Thus the post-filing art of Draghici suggest there is unpredictability of using arrays that have not been verified for clinical use. It is noted that the performing microarray analysis is not the issue, the issue is being able to predictably detect breast cancer or Alzheimer's based on the array data, when the specification nor prior art has clearly identified the sequences claimed can be used to identify these disease.

The response further assert the instant invention allows diagnose of disease state from samples of tissues not directly involved in the disease. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not require diagnose of disease state from samples of tissues not directly involved in the disease, thus the argument is beyond the scope of the claimed invention.

The response further asserts the specification, page 4, lines 25-33, teaches the claimed probes corresponding to altered gene expression in normal versus control

subjects. This has been reviewed but is not considered persuasive as page 4 of the amended specification teaches, "It has been suggested that a pool of tumour tissues that appear to be pathogenetically homogeneous with respect to morphological appearances of the tumour may well be highly heterogeneous at the molecular level (Alizadeh, 2000, supra), and in fact might contain tumours representing essentially different diseases (Alizadeh, 2000, supra; Golub, 1999, supra). For the purpose of identifying a disease, condition, or a stage thereof, any method that does not require clinical samples to originate directly from diseased tissues or cells is highly desirable since clinical samples representing a homogeneous mixture of cell types can be obtained from an easily accessible region in the body. " Thus the cited portion of the specification does not talk about the claimed probes and the argument is unpersuasive.

The response then correctly identifies that methods of making array on solid supports is known. The examiner concurs with this and notes the instant rejection is not based on making the array, but associating the data obtained from the use of an array with a disease state.

The response directs the examiner to numerous parts of the specification in which the actual steps of performing the array are described and based on comparison to a standard or non–control sample. The examiner again concurs that these methods are known, however it is unpredictable to use a collection of 351probes to detect breast cancer or Alzheimer's when the specification only teaches probe sets for such method that are larger and range from 1435 probes to 730 probes. Further the specification does not specifically disclose the instant combination of probes were used in diagnosis

or even the probes that are required for diagnosis and the amendment to the specification has changed the SEQ ID NO associated with the clone ID as well as deleting over 100 clone ID that were previously indicated as informative suggesting the initial disclosed clone ID and probes were not predictable.

The response continues that one of skill in the art understands that the increased or decreased expression relative to a healthy individual. The examiner concurs that the artisan could predictably compare gene expression between healthy and disease individual, however the artisan would not be able to predictably associate these changes with disease states due to the unpredictability taught by Orr and Draghici in view of the New matter objection and the breadth of the newly amended claims.

The response on pages 24-25, asserts that normalization and background subtraction are common and done in the art. Once again the examiner concurs.

On page 26 the response asserts that Cheung and Wu are merely concerned with identifying informative genes which is provided by the instant specification. This argument has been thoroughly reviewed but is not considered persuasive as the claims are not limited to the sequences disclosed, but encompass fragments and fragments with a certain % identity, additionally the specification has not clearly identified the combination of genes presented in the claims are informative in view of the New matter objection.

The response continues by noting that Newton teaches variation in gene expression, but does not address the issue that there is nothing of record to suggest the

collection of probes allows one of skill in the art to detect variations in gene expression that are outside this normal variation that result in diagnosis.

The response further presents the issue of irrelevant genes masking or distorting information from the informative genes. First the examiner notes this is a new issue that was not addressed in the prior action, however, the response appears to be asserting that some of the claimed probes are irrelevant. Irregardless the ability to disregard noise and manipulate data does not demonstrate that one of skill in the art could predictable associate such expression with disease diagnosis. The ability to separate noise from a true signal does not make the association predictable.

The response asserts that the probes of table 2b encompass the claimed probes. This argument has been thoroughly reviewed but is not considered persuasive as in view of the new matter objection to the specification it is unclear which probes are informative. It is noted that table 2 submitted on 5/19/2005 did not recite the combination of claimed SEQ ID NO, however the specification submitted 10/3/2008 contains these sequences. It is thus unpredictable which sequences are informative. It is again noted that MPEP 2163.07 II states:

An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction.

The amendment submitted 10/3/2008 to the tables of 5/19/2005 do not constitute obvious errors nor do the corrections submitted demonstrate these corrections were obvious.

The response further asserts that example 3 of the specification demonstrates that 345 probes were used to generate the figure 9. The response states, "The use of the 345 probes in Example 3 is not significantly different from the use of the claimed 351 probes. Accordingly, one of ordinary skill in the art would appreciate and recognize that the use of similar set of probes of approximately the same size would be unlikely to have any significant impact on the outcome or reliability of the classification model for diagnosis." Thus the response notes that the probes of example 3 are not significantly different, but is noting there are differences. Thus the response suggests that example 3 does not use the claimed probes. Further the response asserts that using probes approximately the same size would not impact the outcome. This argument has been thoroughly reviewed but is not considered persuasive as the claims are not drawn to probes of approximately the same size, but probes as small as 10 bases, that depending on the probe being examined could be any nucleic acid sequence as discussed previously.

Further the response has presented a Declaration under 37 CFR 1.132 from the inventor Praveen Sharma. The declaration states that the 351 sequences in claim 2 (i.e. table 2b) were used in example 1 to analyses breast cancer samples. The declaration continues that figure 8 was obtained by use of data from 345 probes. The declaration states, "This data illustrates that very similar results are obtained using the probes as claimed compared to the slightly different sets of probes which were used for the sample analyses in the application as filed. This illustrates that the probes as claimed are suitable for diagnosis of breast cancer." The declaration has been

thoroughly reviewed but is not considered persuasive as the claims encompass not only the probes of claimed, but fragments of at least 10 nucleotides with 80% or fragments of 10 nucleotides that are completely complementary and thus are of different scope than the claimed invention. Further due to the New Matter objection to the amended specification 10/3/2008, it is unclear which SEQ ID NO are informative and comprise Table 2b.

The response continues by directing the examiner to Metzler and identifying that gene expression analysis is not unpredictable. This argument have been thoroughly reviewed but are not considered persuasive as the unpredictability is drawn to the association of gene expression pattern with breast cancer or Alzheimer's. The cited teachings of Metzler (introduction and conclusions) provide no guidance that the 351 claimed sequences are predictably able to diagnose breast cancer.

The response on page 28 asserts that the claimed combination of probes are informative, this in view of the new matter objection is not persuasive as discussed above. The response further asserts that 139 informative probes were selected for breast cancer diagnosis and 192 probes were selected for Alzheimer's diagnosis from larger training sets. First the examiner notes that table 7 indicates the 139 probes were used for breast cancer, however does not teach the sequences used and teaches there was a 20% error rate. Further the specification lists in table 2a 77 probes and thus does not disclose the combination of 351 probes.

The response continues by asserting that the large scale gene expression studies have been used to selective informative probes from thousands of genes

expressed in a cell. The response asserts that 139 informative probes have been selected for breast cancer diagnosis as exemplified in example 1 and table 2. First there are two table 2, one that lists 77 probes and another that lists 350 probes (clone ID) and 351 sequences. Thus the arguments are not commensurate with the disclosure. Second in view of the New matter objection to the specification it is unclear which probes were part of table 2. Further in view of claims being to fragments of 10 nucleotides or more with 80% identity or fragments that are complementary to at least 10 nucleotides the claimed invention is broader than that disclosed in table 2.

In light of the breadth of the claims and unpredictability of the art of associating gene expression with a phenotype the claims are unpredictable as filed. Further the claims are unpredictable in view of the New Matter Objection to the specification.

Claim Rejections - 35 USC § 102-Maintained

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 2, 4, 9, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Ahr et al (Journal of Pathology (2001) volume 195, pages 312-320).

This rejection is presented to the breadth of the composition claimed oligonucleotide probe set. This rejection does not contradict the enablement rejection as it is directed to the structural limitations of the claims.

Amended claim 2 is drawn to a set of oligonucleotide probes consisting of not more than 1000 oligonucleotides and said set comprising the 351 oligonucleotides having the sequences set forth in the recited SEQ ID NO, with the proviso that any of the said 351 oligonucleotides may be replaced with (i) an oligonucleotide fragment of the respective oligonucleotide being replaced, which fragment is at least 15 nucleotides in length; (ii) an oligonucleotide having a sequence entirely complementary to the respective oligonucleotide being replaced, or to a fragment thereof which is at least 10 nucleotides in length or (iii) an oligonucleotide having at least 80% identity to the respective oligonucleotide being replaced or to a fragment thereof which is at least 10 nucleotides in length.

Embodiment (i) is drawn to replacing the oligonucleotide with “any” oligonucleotide fragment of respective oligonucleotide being replaced, which fragment is at least 15 nucleotides in length. Thus the claim broadly encompasses replacing "any" fragment of oligonucleotides claimed by SEQ ID NO with any fragment that is at least 15 nucleotides in length. Thus embodiment (i) of claim 2 broadly encompasses any nucleic acid, as it is replacing any fragment of SEQ ID NO with any oligonucleotide that is at least 15 nucleotides in length. Thus this encompasses using any nucleic acid sequence.

With respect to claims 2, 4, 9, and 13, Ahr teaches low density cancer blot of 588 genes (see page 313, 2nd column, top paragraph). The 588 probes of Ahr thus contain at leat 351 probes that have 2 nucleotides that are complementary to the recited SEQ ID NO. Ahr thus teaches an array of more than 351 oligonucleotides probes, but less than 1000 oligonucleotide probes. The 588 probes of Ahr comprise at least 351 oligonucleotide probes with at least 2 nucleotides complementary to the recited SEQ ID NO and anticipate the instant claims.

Response to Arguments

The response asserts that Ahr does not specifically disclose the claimed oligonucleotide probes. This argument has been thoroughly reviewed but is not considered persuasive as the claims are not limited to the disclosed sequences, but as stated in the claim interpretation above embodiment (i) broadly encompasses replacing any fragment of the claimed sequences with any oligonucleotide longer than 15 bases, which broadly encompasses any nucleic acid sequence. Thus as the claims require at least 351 oligonucleotides and less than 1000 oligonucleotides, that can be of any sequence the claims are anticipated by Ahr.

Summary

No claims are allowed.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Sarae Bausch/
Primary Examiner, Art Unit 1634